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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,624	12/06/2005	Peter Bromley	GRT/2590-143	2816

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NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
MAKAR, KIMBERLY A	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,624	BROMLEY, PETER	
	Examiner	Art Unit	
	Kimberly A. Makar	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *2000116*.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Interview Summary

1. The examiner spoke with Applicant's representative Gary Tanagawa on 2/5/07 regarding the finality status of the office action mailed 01/25/07. After discussion with applicant, and upon further consideration, the finality of the office action dated 01/25/07 is withdrawn.

Response to Arguments

2. Amendments to claims 1-6 by applicant in response dated 11/07/06 are acknowledged. Addition of claims 7-18 by applicant in response dated 11/07/06 are acknowledged. Currently claims 1-18 are pending.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claim 1 is rejected under 35 U.S.C. 102(b) as being taught by Yoo et al (The Activation of the Rat Copper/Zinc Superoxide Dismutase Gene by Hydrogen Peroxide through the Hydrogen Peroxide-responsive Element and by Paraquat and Heat Shock through the Same Heat Shock Element. The Journal of Biological Chemistry, 1999. 274(34): 23887-23892.) Claim 1 recites a method for producing protein in human hepatocytes cells, said method comprising: providing a DNA construct in which a gene encoding a protein of interest is operably linked to a modified heat-inducible promoter; introducing said DNA construct into a human hepatocyte cell line, either by transformation or by transfection, to form a transformed or transfected cell line respectively; and subjecting said transformed or transfected cell line to a transient increase in temperature and permitting protein translation to occur after the temperature has been returned to growth temperatures, whereby the production of said protein of interest occurs.

5. Yoo et al teaches a minimal heat shock element of the SOD1 promoter that is operably linked to a heterologous thymidine kinase promoter which is further operably linked to a Chloramphenicol acetyltransferase reporter gene which is capable of expressing the reporter gene in response to heat shock (see figure 5). The vector is transfected into human hepatocyte cell line HepG2. Yoo et al teaches that the cells are subjected to heat shock of 42°C for 1 hour, and the CAT assay is performed 2 hours after heat shock (see page 23889, column II, last paragraph though page 23890 first

column, first paragraph, and the legend for figure 5.) He also teaches that the cells are reequilibrated to 37°C for 1 hour following heat shock (page 23891, column 1). Thus Yoo teaches the claimed invention.

6. Claim 10 is rejected under 35 U.S.C. 102(e) as being taught by Tsang el al (US 2003/0207832). Claim 10 recites an expression comprising: a bacterial origin or replication, a Zeocin resistance gene selectable by zeocin antibiotic in both prokaryoticic and eukaryotic cells, and a heat-inducible promoter operably linked to a gene encoding a protein of interest.

7. Tsang teaches an expression vector comprising a modified heat inducible promoter comprising a heat shock promoter and a second promoter operably linked to the polynucleotide of interest in a cell (claim 22). Specifically Tsang teaches that the vector include the Hi-Hot promoter (see Example 6 and figure 11). Tsang teaches that the DNA construct comprises a zeocin selectable marker which is used in the selection of transformants (page 10, paragraph 0012) and would be capable of selection by zeocin in either prokaryotic or eukaryotic cells. Tsang teaches that the vectors are used to express therapeutic proteins including CNTF, BDNF, GDNF, IGF-1, and angiogenesis inhibitors (page 9, paragraphs 0098-0099). Thus Tsang teaches the claimed invention.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 2-9, 11-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoo et al (The Activation of the Rat Copper/Zinc Superoxide Dismutase Gene by Hydrogen Peroxide through the Hydrogen Peroxide-responsive Element and by Paraquat and Heat Shock through the Same Heat Shock Element. The Journal of Biological Chemistry, 1999. 274(34): 23887-23892) as applied to claim 1 above, and further in view of Tsang el al (US 2003/0207832). Claims 2-9, 11-18 recite a method for producing protein in human hepatocytes cells, said method comprising: providing a DNA construct in which a gene encoding a protein of interest is operably linked to a modified heat-inducible promoter; introducing said DNA construct into a human hepatocyte cell line, either by transformation or by transfection, to form a transformed or transfected cell line respectively; and subjecting said transformed or transfected cell line to a transient increase in temperature and permitting protein translation to occur after the temperature has been returned to growth temperatures, whereby the production of said protein of interest occurs wherein the modified heat-inducible promoter is the Hi-Hot promoter (claim 2). The method is further limited wherein the human hepatocyte cell line is stably transfected with said DNA construct (claim 3) and wherein the gene encodes a therapeutic protein (claim 4). The method is further limited wherein the therapeutic protein is selected from the group consisting of interferons, interleukins, blood clotting factors, insulin, growth hormone, urokinase, EPO, TPA, FSH, somatostatin, antibodies, DNAse, myoglobin and pro- and anti-angiogenesis factors

(claim 5). The method is further limited wherein the gene encodes a natural liver protein (claim 6) and where the gene encodes a protein of veterinary interest (claim 7). The method is further limited wherein the DNA construct further comprises a Zeocin resistance gene or is selected by zeocin antibiotic (claims 8 and 9).

10. Claim 11 recites a method for producing protein in human hepatocyte cells, said method comprising: providing a DNA construct in which a gene encoding a protein of interest is operably lined to a heat-inducible promoter, introducing said DNA construct into an immortalized human hepatocyte cell line by stable transfection to form a stably transfected and immortalized cell line, growing said stable transfected and immortalized cell line at a temperature, and subjecting said stably transfected and immortalized cell line to a transient increase in the temperature to induce said promoter; thereby producing said protein of interest. The method is further limited wherein the heat inducible promoter is the Hi-Hot promoter (claim 12) and wherein the gene encodes a therapeutic protein (claim 13) selected from the group consisting of interferons, interleukins, blood clotting factors, insulin, growth hormone, urokinase, EPO, TPA, FSH, somatostatin, antibodies, DNAse, myoglobin and pro- and anti-angiogenesis factors (claim 14). The method is further limited wherein the gene encodes a natural liver protein (claim 15) and where the gene encodes a protein of veterinary interest (claim 16). The method is further limited wherein the DNA construct further comprises a Zeocin resistance gene or is selected by zeocin antibiotic (claims 17 and 18).

11. Yoo et al teaches a method for producing protein in human hepatocyte cells, said method comprising: providing a DNA construct in which a gene encoding a protein of

interest is operably linked to a modified heat-inducible promoter; introducing said DNA construct into a human hepatocyte cell line, either by transformation or by transfection, to form a transformed or transfected cell line respectively; and subjecting said transformed or transfected cell line to a transient increase in temperature and permitting protein translation to occur after the temperature has been returned to growth temperatures (see above). Analysis of Yoo's heat shock inducible vector experiments reveals that heat shock stress garners the highest reporter protein yield in all experiments when compared to two other types of stresses applied (heat, H_2O_2 and paraquat) to the cells (see figures 1, 2, 3, and 4). Yoo does not teach that the heat-inducible promoter is the Hi-Hot promoter, nor that the vector encodes a therapeutic or a native liver protein, nor that the vector is selected by zeocin resistance, nor that the proteins are of veterinary interest.

12. 13. Tsang et al teaches a method of expressing a selected polynucleotide of interest under the control of a modified heat inducible promoter comprising a heat shock promoter and a second promoter operably linked to the polynucleotide of interest in a cell (claim 22). Specifically Tsang teaches that the vector includes the Hi-Hot promoter (see Example 6 and figure 11). Tsang teaches that the method of gene transfer includes transfection (page 12, paragraph 136). Tsang teaches that the method includes the heat-shock conditions of the transfected cell which can comprise temperature ranges of 37°C to 42°C. Tsang teaches the method in which transfected cells are cultured at 37°C and subjected to 41-42°C, 1 hour heat shock periods and subsequently returned to 37°C in Interleukin amplifier experiments (page, 19, paragraph 220). Tsang teaches that

the recombinant vectors can be expressed in human cell lines DU-145, MCF (page 17, paragraph 193). Tsang teaches that the DNA construct comprises a zeocin selectable marker which is used in the selection of transformants (page 10, paragraph 0012). Tsang teaches the method of transformation of the vector may be stably integrated into the genome of the recipient cell (page 12, paragraph 0137) and that a target cell for the introduction of the DNA construct is a liver cell (page 15, paragraph 0175). Tsang teaches that the vectors are used to express therapeutic proteins including CNTF, BDNF, GDNF, IGF-1, and angiogenesis inhibitors (page 9, paragraphs 0098-0099). Tsang teaches that the vector can encode for interleukins and the natural liver proteins Interferon-a (INF-a) and Intercellular adhesion molecule 1(I-CAM 1) (claim 35).

13. The instant specification fails to define a "protein of veterinary interest." There is no mention of the phrase "protein of veterinary interest" in the specification, other than original claim 5 and newly presented claim 16. Using the broadest possible interpretation, the phrase "protein of veterinary interest" is being defined as a therapeutic protein that is expressed in an animal. Tsang teaches the expression of therapeutic proteins in mice (see examples 4 and 7). Tsang teaches that some current cancer therapies include both gene therapy and hyperthermia. However he teaches that hyperthermia occurs at temperatures above those in which normal gene therapy occurs, thus not enabling the gene therapy to be sustained. He also teaches that hyperthermia treatment enhances the effects of radiation therapy. He further teaches that the development of using heat-inducible promoters responsive to temperatures at 42°C is a way treat cancer, thus combining the advantages of gene therapy and

hyperthermia in traditional cancer therapies while overcoming known obstacles (page 1, paragraphs 0006-0010).

14. A skilled artisan would have been motivated to combine the teaching of Yoo on a method of producing protein in human hepatocyte cell lines, said method comprising: providing a DNA construct in which a gene encoding a protein of interest is operably linked to a modified heat-inducible promoter; introducing said DNA construct into a human hepatocyte cell line, either by transformation or by transfection, to form a transformed or transfected cell line respectively; and subjecting said transformed or transfected cell line to a transient increase in temperature and permitting protein translation to occur after the temperature has been returned to growth temperatures where heat-shock is shown to cause the highest reporter protein results with the teaching of Tsang on a method of producing stable cell lines in human cells, including liver cells, said method comprising: providing a DNA construct in which a gene encoding a therapeutic or veterinary protein of interest operably linked to a Hi-Hot promoter; introducing said DNA construct into a human cell line, either by transformation or by transfection, to form a transformed or transfected cell line respectively; and subjecting said transformed or transfected cell line to a transient increase in temperature and permitting protein translation to occur after the temperature has been returned to growth temperatures wherein the DNA construct comprises a Zeocin resistant gene because Yoo teaches that the heat-shock response garners the highest reporter protein yield, signaling that the promoter responds best to heat shock, while Tsang shows that his system combines several known cancer therapies while over-coming known obstacles

in the cancer field regarding gene-therapy and hyperthermia. Thus it would have been obvious to combine the method of Yoo on producing proteins in human HepG2 cell lines in response to a modified heat-inducible promoter wherein the cells are transiently subjected to an increase in temperature further with the teaching of Tsang on the method of producing therapeutic proteins in human cell lines using the Hi-Hot heat-inducible promoter after subjecting the stable cell lines to a transient increase in temperature because while Tsang teaches that his system can be used in liver cells, Yoo teaches that his heat-inducible system works in liver cell lines, and the heat-inducible system has the highest stress response of the three types of stresses tested one would have wanted to improve the method of Yoo by implementing a cancer treating method that overcomes known obstacles in the realm of cancer treatment. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

Conclusion

15. No claims are allowed. Any rejection not mentioned in this office action is withdrawn. The removal of all prior rejections render the arguments of applicant in response dated 11/07/06 moot.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Makar, Ph.D. whose telephone number is 571-272-4139. The examiner can normally be reached on 8AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kam/06/11/07

DAVID GUZO
PRIMARY EXAMINER